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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,302	09/15/2005	Michael Hagen	AM100485	5958

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WYETH
PATENT LAW GROUP
5 GIRALDA FARMS
MADISON, NJ 07940

EXAMINER	
HINES, JANA A	

ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,302	HAGEN, MICHAEL	
	Examiner	Art Unit	
	JaNa Hines	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *12-51 and 63-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 52-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/5/07 & 9/15/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group A in the reply filed on March 18, 2008 is acknowledged.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on September 15, 2005 and October 5, 2007 were filed. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

3. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

4. The use of the trademarks STIMULON™ QS-21, MPL™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 10, 52 and 61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The preamble of the claims is drawn to a method of immunizing a mammalian host, however the recited steps within the method do not state what the host is immunized from. There is no correlation step which correlates the cholera holotoxin and the covalently associated antigen to immunizing the host against a particular antigen. Therefore the metes and bounds of the claim are indefinite and clarification is required to overcome the claims.

b) The claim scope of claims 10 and 61 is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name STIMULON™, QS-21™, MPL™ is used to identify/describe a particular material, and accordingly, the identification is indefinite. Furthermore, the use of trademarks is improper since products identified by trademarks are within the sole control of the trademark owner and are subject to change by said owner at their discretion.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 8, 9, 52, 56, 59, 60 and 62 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10, 13, 14,15, 24 and 25 of U.S. Patent No. 7,384,640 in view of Agren et al., (J. of Immunol. 1999. 162(2): 2432-2440).

The claim 1 of US Patent 7,384,640 are drawn to an antigenic composition comprising: (a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and (b) an effective adjuvating amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the

wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said organism. The claim 10 of US Patent 7,384,640 are drawn to an antigenic composition comprising: (a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and (b) an effective adjuvating amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said organism; and (c) a second adjuvant in addition to the mutant cholera holotoxin. Claim 13 is drawn to a method comprising administering to a host the antigenic composition comprising (a) at least one antigen from a pathogenic organism selected from the group consisting of a bacterium, a virus, a fungus and a parasite; and (b) an effective adjuvating amount of a mutant cholera holotoxin, wherein the mutant holotoxin has reduced toxicity compared to wild-type cholera holotoxin, and has a histidine which replaces the glutamic acid which naturally occurs at position 29 of the A subunit of the wild-type cholera holotoxin and wherein said mutant holotoxin enhances the immune response in a vertebrate host to said organism. Claims 14, 15, 24 and 25 are drawn to the composition comprising more than one antigen; the substituted amino acid at position 29 being histidine; the composition further comprising a diluent or carrier; and comprising a second adjuvant.

Claim 1 of the instant application 10/549,302 are drawn to an immunogenic composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen. Claims 8 and 9 are drawn to the composition further comprising additional non-covalently associated antigens; and one or more adjuvants.

Claim 52 is drawn to a method of immunizing a mammalian host comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen. Claims 56, 59, 60 and 62 are drawn to: the residue being a histidine residue; the composition further comprising additional non-covalently associated antigens; the composition further comprising one or more adjuvants; and the composition further comprising a pharmaceutically acceptable carrier. However US Patent 7,384,640 do not teach that the cholera holotoxin and the antigen are covalently associated.

Agren et al., teach the adjuvanticity of the Cholera Toxin A1-based gene fusion protein; wherein the cholera and the antigen are covalently associated. Agren et al., teach the A1 subunit with a single amino acid change having comparable adjuvant function with that of the wild-type holotoxin (page 2432, col.1). Agren et al., teach a

major breakthrough in immunomodulation and vaccine adjuvant design where they constructed a gene fusion that combined the enzymatic activity of the A1 subunit of CT with a B cell targeting moiety from an IgG-binding fragment of *Staphylococcus aureus* protein (page 2432, col. 2). The immunomodulator fusion protein composition was found to be completely nontoxic *in vitro* and *in vivo*. Agren et al., the administering the composition to mice (page 2433, col. 2). Agren et al., teach a promising now strategy for vaccine adjuvant design and proves the concept that novel immunomodulators can be constructed as gene fusion proteins that target powerful bacterial enzymes, thereby avoiding harmful side effects (page 2432, col. 2). Agren et al., teach the construction of several mutants wherein the site mutations are at positions 7, 109 and 112 (page 2433, col.1). Thus, Agren et al., teach the ADP-ribosyltranferase activity as well as the Ig-binding ability which are critically required for the adjuvant function of the covalently associated CT-A and antigen (page 2433, col. 1).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply Agren et al's covalently associated cholera holotoxin to US Patent 7,384,640's composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen, and method of immunization in order to provide novel immunomodulators constructed as covalently associated holotoxin and antigens which target powerful bacterial enzymes. One of ordinary skill in the art would have a reasonable expectation of success by incorporating covalently associated mutated CT and an antigen, because

no more than routine skill would have been required to covalently associated to the CT and the antigen when the art already teaches their co-administration. Furthermore, no more than routine skill would have been required to incorporate the covalently associated cholera holotoxin and the antigen of Agren et al., for the available and functionally equivalent immunogenic composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29 of SEQ ID NO:2, since Agren et al., teach the ADP-ribosyltranferase activity as well as the Ig-binding ability are critically required for the adjuvant function of the mutant cholera holotoxin and antigen to advantageously achieve increased immunogenicity while having reduced toxicity.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-11 and 52-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jobling et al., (WO 00/18434) in view of Agren et al., (J. of Immunol. 1999. 162(2): 2432-2440).

The claims are drawn to an immunogenic composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen. The claims are also drawn to a method of immunizing a mammalian host comprising administering to the host an immunogenic amount of a composition comprising a cholera holotoxin (CT) and an antigen covalently associated with the CT, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid residue 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen.

Jobling et al., teach a composition comprising a mutant form of the Cholera toxin (CT) holotoxin that has reduced toxicity compared to a wild-type CT in an antigenic composition in order to enhance in a vertebrate host to a selected antigen from a pathogenic bacteria, virus, fungus or parasite (page 3-4, lines 31-3). Jobling et al., teach a point mutation a amino acid 29 of the A subunit wherein the glutamic acid residue is replaced by an amino acid other than aspartic acid (page 4, lines 4-8). The amino acid residue 29 is histidine (page 4, line 9). Jobling et al., teach other mutations within the A subunit are known, including positions 7, 11, 110 and 112 (page 10, lines 15-23). Jobling et al., teach encoded polynucleotides comprising the nucleic acid sequence of SEQ DIN O:1 wherein the sequences has a genetic modification of at least codon 29 of SEQ ID NO:1. See Example 1 teaching the oligonucleotide derived mutants created in plasmids and the construction of the plasmid encoding CT- with a

nonconservative amino acid substitution (glutamic acid to histidine) at position 29 in the A subunit (See Example 1, at page 44).

Jobling et al., teach composition further comprises a diluent or carrier (page 4, lines 16-17). Jobling et al, teach the compositions further comprises adjuvants such as STIMULON™ QS-21, MPL™ (3-O-deacylated monophosphoryl lipid A), aluminum phosphate, aluminum hydroxide, IL-12, (page 39-40, lines 28-2). The vaccine antigens are from a wide variety of pathogenic microorganisms where the antigen comprises a one or more saccharides, proteins, protein subunits, or fragments, poly- or oligonucleotides, or other macromolecular components (page 40, lines 3-13). Jobling et al., teach that the compositions may contain more than one antigen from the same or different pathogenic microorganisms (pages 40-41). Jobling et al., teach the antigen and the mutant CT are administered at the same time (page 39, lines 15-17).

However Jobling et al., do not teach that the cholera holotoxin and the antigen are covalently associated.

Agren et al., teach the adjuvanticity of the Cholera Toxin A1-based gene fusion protein; wherein the cholera and the antigen are covalently associated. Agren et al., teach the A1 subunit with a single amino acid change having comparable adjuvant function with that of the wild-type holotoxin (page 2432, col.1). Agren et al., teach a major breakthrough in immunomodulation and vaccine adjuvant design where they constructed a gene fusion that combined the enzymatic activity of the A1 subunit of CT with a B cell targeting moiety from an IgG-binding fragment of *Staphylococcus aureus* protein (page 2432, col. 2). The immunomodulator fusion protein composition was found

to be completely nontoxic *in vitro* and *in vivo*. Agren et al., the administering the composition to mice (page 2433, col. 2). Agren et al., teach a promising now strategy for vaccine adjuvant design and proves the concept that novel immunomodulators can be constructed as gene fusion proteins that target powerful bacterial enzymes, thereby avoiding harmful side effects (page 2432, col. 2). Agren et al., teach the construction of several mutants wherein the site mutations are at positions 7, 109 and 112 (page 2433, col.1). Thus, Agren et al., teach the ADP-ribosyltranferase activity as well as the Ig-binding ability which are critically required for the adjuvant function of the CT-A fusion protein (page 2433, col. 1).

Therefore it would have been prima facie obvious at the time of applicants' invention to apply Agren et al's covalently associated mutant cholera holotoxin and antigen to Jobling et al, immunogenic composition comprising a cholera holotoxin (CT) and an antigen, wherein the CT comprises an A subunit (CT-A) having a mutation of at least amino acid 29 of SEQ ID NO:2, wherein the mutation is not an aspartic acid, wherein the CT increases immunogenicity of the antigen, and method of immunization in order to provide novel immunomodulators constructed as gene fusion proteins that target powerful bacterial enzymes. One of ordinary skill in the art would have a reasonable expectation of success by incorporating covalently associated mutated CT and an antigen, because no more than routine skill would have been required to covalently associated the CT and the antigen when the art already teaches co-administration; the avoidance of harmful side effects; and the diverse application for vaccine development when the same single amino acid mutation is well known in the

art. Furthermore, no more than routine skill would have been required to incorporate the covalently associated cholera holotoxin and the antigen of Agren et al., for the available and functionally equivalent immunogenic composition of Jobling et al., comprising a cholera holotoxin and an antigen, wherein the CT-A has a mutation of at least amino acid 29 of SEQ ID NO:2, since Agren et al., teach the criticality of both ADP-ribosyltranferase activity and Ig-binding ability for the adjuvant function of the covalently associated CT-A to advantageously achieve increased immunogenicity while maintaining it reduced toxicity characteristic.

Conclusion

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 571-272-0859. The examiner can normally be reached Monday thru Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/JaNa Hines/
Examiner, Art Unit 1645

/Mark Navarro/

Primary Examiner, Art Unit 1645